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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/687,996	10/17/2003	Lothar Steidler	2676-6096US	1934

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EXAMINER	
PROUTY, REBECCA E	
ART UNIT	PAPER NUMBER
1652	

NOTIFICATION DATE	DELIVERY MODE
11/30/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTOMail@traskbritt.com

Office Action Summary	Application No.	Applicant(s)	
	10/687,996	STEIDLER, LOTHAR	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,10-15,17-19,21-26,29-35,37-39,42 and 65-72* is/are pending in the application.

4a) Of the above claim(s) *11,18,19 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-7,10,12-15,17,21-26,29,30,32,34,35,37-39,42 and 65-71* is/are rejected.

7)☐ Claim(s) *31 and 33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 2, 4, 8, 9, 16, 20, 27, 28, 36, 40, 41, and 43-64 have been canceled. Claims 1, 3, 5-7, 10-15, 17-19, 21-26, 29-35, 37-39, 42, 65-68 and newly presented claims 69-72 are at issue and are present for examination.

Claims 11, 18, 19 and new claim 72 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on March 30, 2006.

Claims 10, 21, 32, 34, and 67 are objected to because of the following informalities:

- claim 10 needs the word “the” inserted following “wherein” in line 2
- claim 21 is grammatically awkward in “comprises lacking an active”. It is suggested that “comprises lacking” be replaced with “lacks” and the word “comprises” be inserted prior to “a gene encoding”
- claim 32 needs the word “an” inserted following “lacks” in line 2
- claim 34 would be clearer if “of said parent strain" were inserted at the end of the claim and

- claim 67 is grammatically awkward in "comprising lacking an active". It is suggested that "comprising" be deleted from this phrase and the word "comprising" be inserted prior to "a gene encoding".

Appropriate correction is required.

Claims 22 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is confusing in the recitation of "wherein said parent strain comprises SEQ ID NO:3 and SEQ ID NO:5 as taken literally this would require the parent strain to comprise two different thymidylate synthase genes as the same thymidylate synthase gene cannot comprise both sequences simultaneously. It is presumed applicants actually intended "SEQ ID NO:3 or SEQ ID NO:5".

Claim 68 is incomplete in depending from cancelled claim 2.

Claim 68 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected,

to make and/or use the invention. The rejection was explained in the previous Office Action.

Applicants argue that MG1363 is well-known and widely-available in the art, GenBank has a record of the organism's complete genome and a search of NCBI's PubMed database reveals an abundance of research using said strain but if *Lactococcus* strain MG1363 is unavailable through, e.g., ATCC, or the strain is otherwise unavailable, and this is the last remaining obstacle to allowing the application, a deposit will be made. This is not persuasive as applicants have not provided any evidence that the strain is in fact publicly available, a search of the online ATCC bacteria catalog does not show the strain to be available (see enclosed printout) from ATCC and simply having the sequence of the genome of a bacterium does not allow one to make the bacterium. Furthermore, while a statement from applicants that a deposit will be made prior to issuance would be sufficient to withdraw the rejection under *In re Lundak*, applicants statement is not unequivocal that a deposit will be made and does not include a statement that the deposit will meet all requirements of 37 CFR 1.801-1.809.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 5-7, 10, 12-15, 17, 21, 23-26, 29, 30, 32, 34, 35, 37-39, 42, 65-67, and 69-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nilsson et al. (WO00/01799) in view of Steidler et al. (WO00/23471) and Curtiss III (US Patent 4,888,170). The rejection is explained in the previous Office Action.

Applicants argue that no motivation would have existed at the time of the invention to combine Nilsson, Steidler, and Curtiss to arrive at the claimed *Lactococcus* mutant that comprises a gene encoding a heterologous therapeutic molecule and expresses the molecule. However, this is not persuasive as the need for containment systems for genetically engineered bacteria, particularly those which are intended for therapeutic purposes and therefore release into the environment, was a well known problem in the art at the time of the instant invention. Curtiss III teach that ΔthyA bacteria that require a particular nutrient can be used to create carrier microbes incapable of surviving in nature but still capable of delivering a heterologous protein to the intestinal mucosa of a mammal. As

such a skilled artisan would have readily realized the potential use of these bacteria as carriers for other heterologous proteins as well as the particular antigens used by Curtiss III. As such a skilled artisan would have readily understood the applicability of the ΔthyA bacteria to the disclosure of Steidler et al. which teaches the use of genetically engineered *Lactococcus lactis* strains for delivery of a therapeutic protein to the intestinal mucosa and thus would have been motivated to use a ΔthyA *Lactococcus lactis* strain. Since Nilsson et al. in fact teach such a strain, a skilled artisan would have found it obvious to use this strain and transform it with the therapeutic gene of Steidler et al. It is irrelevant that the ΔthyA *Lactococcus lactis* strain taught by Nilsson et al. was developed for a different purpose as the disclosure of Curtiss III teaches the use of ΔthyA bacteria for containment of genetically engineered bacteria. As stated in KSR, "it is common sense that familiar items may have obvious uses beyond their primary purposes, and a person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle" (*KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1391). As such merely because Nilsson et al. did not teach the use of their ΔthyA *Lactococcus lactis* strain for containment of genetically engineered bacteria, a skilled artisan would not

have found it non-obvious to use it for this in view of the teaching of Curtiss III of using ΔthyA bacteria for this purpose.

Applicants argue that Curtiss' work is performed in a mouse model but a mouse model is recognized by those of skill in the art as a particularly poor system for extrapolating results to mammals in general, as mice are a system unusually rich in thymidine. Applicants cite Table 2 of Nottebrock et al. (see applicants IDS) in support of this statement. However, the cited document does not in fact support applicants statement as Nottebrock et al. disclose that mouse urine and blood have substantially higher thymidine levels than other mammals blood and urine but not that mouse intestines have substantially higher thymidine levels than other mammals intestines. A skilled artisan would readily expect the intestines of all mammals to have high levels of thymidine as the intestines are the main location of digestion of all food. All food used by mammals comprise DNA whose digestion will result in the production of thymidine. Thus differences in the levels of thymidine in other tissues/fluids of mammals between mice and humans would not have led a skilled artisan to believe that there would not be sufficient thymidine present within the intestines of other mammals to support growth of a ΔthyA

bacteria as disclosed by Curtiss III. It is noted that Curtiss III clearly believe that the mouse is a suitable model system for their invention as clearly the intended use of the engineered bacteria disclosed by Curtiss III is for the vaccination of humans.

Applicants argue that the object of Curtiss' invention is to raise an immune response to the protein delivered by the bacteria and Curtiss particularly shows at column 20 that immunogenicity increases with *thyA* inactivation and that in view of this a skilled artisan would not be motivated to use these bacteria for the delivery of a therapeutic protein as the last thing an artisan would want when delivering a therapeutic protein is an increase in immunogenicity. However, this is not persuasive because the data of Curtiss does not clearly show that immunogenicity increases with thyA inactivation. First it is noted that applicants are incorrect that Curtiss' χ3115 strain includes a ΔthyA mutation (see column 17 lines 63-69 and Table 2). Only the χ3137 strain is a ΔthyA mutant strain. As such any discussion of Table V of Curtiss III is irrelevant. Furthermore, comparing Tables III and IV it is noted that only a single data point (i.e., one of two measurements of antibody at 22 days post challenge in saliva) differs substantially at all and this same difference was not repeatable as the other

measurement of the same data point was 10 fold lower. Furthermore the peak antibody response seen in serum between the control and the mutant strain was substantially similar, as was the peak response in saliva if one ignores the single apparently anomalous data point). At best the results of Curtiss III indicate that there is a possibility that immunogenicity increases with thyA inactivation but the results are far from making it clear that this is the case. As such, as skilled artisan would not have found the results of Curtis III to teach away from the instant invention.

Applicants argue that because Curtiss III focus entirely on the expression of antigenic proteins, intended to induce an immune response, that one of ordinary skill in the art would not apply the teachings therein to the expression of a heterologous therapeutic protein. However, this is not persuasive as this argument relies on the fact that Curtiss III did not literally acknowledge that an antigenic protein is merely one example of a heterologous protein that one might choose to genetically engineer into a bacterium for expression within the intestinal mucosa and fails to provide any reason (beyond those already discussed) why a skilled artisan could not see that the teachings in fact could apply to the broader class.

Applicants argue that because *Lactococcus* is not a pathogenic microorganism, there can be no intention to make *Lactococcus* avirulent. However, while there may be no need to make a recombinant *Lactococcus* strain avirulent, a skilled artisan would have understood that there was sufficient motivation to make a recombinant *Lactococcus* strain that could not survive in nature as all the consequences of releasing genetically engineered microorganisms into the wild are unpredictable. Thus skilled artisans were motivated to make any recombinant strain incapable of surviving outside of the environment it is intended to used within in order to prevent such unforeseen and potentially detrimental consequences.

Applicants argue that Nilsson et al. teach away from use of the *thyA* mutants for containment purposes because containment requires death of the mutant bacteria in the non-permissive conditions (i.e., low thymidine) while the methods of Nilsson require that the mutant bacteria remain viable and metabolically active in the non-permissive conditions. However, Nilsson nowhere teaches that *thyA* mutants remain viable and metabolically active indefinitely and a skilled artisan would clearly not expect this to be the case in the absence of the ability to reproduce as there are no known immortal organisms. The methods of Nilsson et al. only require that the mutant

strains remain viable in the non-permissive conditions for a period of time sufficient to achieve the acidification of milk (30 hours in the methods of Nilsson et al.). In fact Figure 5 of Nilsson et al. shows that most of the acidification occurs within the first 5 hours and the activity is virtually complete within 10 hours and thus the data are not in fact incompatible with the mutant bacteria becoming non-viable even within the period of time of the experiments of Nilsson et al. As such the disclosures of Nilsson et al. do not teach away from using the *thyA* mutants for biological containment purposes as biological containment does not require immediate death of the engineered bacteria but only death within a reasonable period of time to prevent such potentially detrimental consequences such as exchange of genetic information with other organisms etc.

Claims 31 and 33 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim 22 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on

access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Prouty/
Primary Examiner
Art Unit 1652